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EXAMINER	
LIU, SAMUEL W	

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1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,247	BAR-OR, DAVID	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46, 49-53, 81, 186, 194-199, 217-220, 246, 272, 273 and 280-299* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☒ Claim(s) *272 and 273* is/are allowed.

6)☒ Claim(s) *46,49-52,186,194-198,217-220,246,280,282-285,289-292 and 295-299* is/are rejected.

7)☒ Claim(s) *53,199,281,286-288,293 and 294* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/10 & 5/19/10*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 46, 49-53, 81, 186, 194-199, 217-220, 246, 272, 273 and 280-299 are pending.

The amendment filed 5/19/10 which amends claims 46, 81 and 186 has been entered. Claims 1-45, 47-48, 54-80, 82-185, 187-193, 200-216, 221-245, 247-271 and 273-279 were cancelled by the amendment filed 11/20/06. Claims 46, 49-53, 81, 186, 194-199, 217-220, 246, 272-273 and 280-299 are under examination.

IDS

The references listed in IDS filed 1/22/10 and the IDS filed 5/19/10 (except reference "JP2001-346588 which is not in English and has been lined-cross) have been considered by Examiner.

New-Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 81 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement; this is a new matter rejection. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "A kit for contacting a cell, a tissue or an organ …comprising … a container holding a phosvitin or fragment thereof which at least 70% dephosphorylated", which as amended into the claims on 5/19/10, is not supported in the

specification as originally filed. Applicant can either cancel the new matter or point out specification support for the phrase in the specification as originally filed.

Maintained-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[1] Claims 46, 49-52, 186, 194-198, 217, 219, 220, 246, 280, 282-285, 289-292, 295 and 297-299 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds E. C. (US Pat. No. 6780844) in view of Jiang et al. (*J. Agric. Food Chem.* (2000) 48, 990-994).

Reynolds teaches a pharmaceutical composition (col.7, line 4-7) comprising a complex containing phosphopeptide stabilized amorphous calcium fluoride phosphate (col. 2, line 56 and 57, and col. 3, lines 8-11), and teach a pharmaceutical composition comprising said complex wherein the pharmaceutical composition is a dental composition in a form of a gel, solid, powder or cream (col.7, lines 5-10) for treating dental caries or tooth decay (col. 3, lines 55-59), wherein the dental cream is toothpaste (col. 4, lines 27 and 28). Reynolds teaches that their phosphopeptide can be obtained from any source, such as phosphor-acid rich proteins, e.g., "phosphitin" (col. 2, lines 58-60); wherein the "phosphitin" is an alternative name of **phosvitin** (see "*Discussion of art*" [1] and [2]). Reynolds teaches that said the phosphopeptide is a casein protein fragment of SEQ ID NO:2, 3 or 4 wherein all SEQ ID NOs:2, 3 and 4 are partially phosphorylated (see patent claim 3) wherein one out of total five Ser residues (80%) are phosphorylated, i.e., 20% dephosphorylated.

Also, Reynolds teaches that the phosphopeptide stabilizes amorphous calcium phosphate (ACP), and teaches that the stabilized ACP is most soluble (col. 2, lines 14-17) wherein the stabilized and soluble ACP prevents caries and increases calcium bioavailability (col. 2, lines 17-20). These teachings are applied to claims 46, 50, 51, 186, 195-197, 219, 220, 246, 280, 282-284, 289-291 and 297-299.

The topical administration has been suggested (col.7, lines 18 and 19), as applied to claims 217 and 295.

Yet, Reynolds does not expressly teach that the above-disclosed phosphopeptide is phosvitin or fragment thereof nor teaches that the phosphopeptide is partially phosphorylated, e.g., 65% de-phosphorylated.

Jiang et al. teach that the partially phosphorylated (with 35% phosphates retention) phosvitin phosphopeptide ("PPP") inhibits calcium phosphate precipitation wherein 35% phosphate retention which is considered to be equivalent to about 65% de-phosphorylation thereof shows the highest capability of solubilization of the insoluble calcium phosphates (see Figure 5, p. 993, p.994, left col., lines 10-12, and abstract). Also, Jiang et al. teach that "PPP" is useful for a nutraceutical (p. 994, left column, last sentence) wherein the "nutraceutical" composition is a combination of nutrition and pharmaceutical (see Wikipedia (2009, updated) "Nutraceutical", en.wikipedia.org/wiki/Nutraceutical, pages 1-8), and thus, the nutraceutical composition taught by Jiang et al. is considered o be a pharmaceutical composition. The Jiang et al. teachings are applied to claims 46, 50, 51, 186, 195-197, 280, 282-284 and 289-291.

Jiang et al. teach that PPP is obtained from hen egg yolk (page 991, left col., section "Materials"), as applied to claims 49 and 194.

Considering that "65%" read on "about 70%" wherein "about" renders "65%" applicable herein, claims 52, 198, 285 and 292 are included in the rejection.

It would have been obvious to one ordinary skill in the art at the time the invention was made to prepare the pharmaceutical composition such as in a gel or powder form of dental composition which comprises the dephosphorylated (~ 65%) phosvitin or fragment thereof. This is because of the reasons below.

Reynolds has taught that the phosphopeptide can be obtained from any source that includes the known phosphor-acid rich proteins, phosvitin (col. 2, lines 58-60). Insoluble calcium phosphates limit their anticariogenic activity and have poor bioavailability (col. 2, lines 26-35, Reynolds), suggesting importance of solubilization of the calcium phosphates. The phosphopeptides mediated fluoride-amorphous calcium phosphate phase localization at the tooth surface provides superior anticaries efficacy (col. 2, lines 43-48, Reynolds) due to the complex acting as a delivery vehicle that co-localizes calcium ions at a target site (col. 3, lines 48-52). The Reynolds' teachings are applied to claims 46, 49-51, 186, 194-197, 280, 282-284 and 289-191.

One of ordinary skill in the art would have substitute the phosvitin phosphopeptide for casein phosphopeptide and would have used the phosvitin phosphopeptide to form said complex in said pharmaceutical composition. This is because of the following reasons.

(**i**) Reynolds' phosphopeptide is partially phosphorylated, i.e., in the dephosphorylated (20%) state, and Jiang et al. also taught the dephosphorylated phosphopeptide (phosvitin fragment) useful as the pharmaceutical (see above discussion);

(**ii**) Reynolds has taught possibility of substitution of the casein phosphopeptide by the phosvitin phosphopeptide (col. 2, lines 58-60); and

(iii) Jiang et al. have taught that the phosvitin peptide with the 65% de-phosphorylated produces the highest degree of solubilization of calcium phosphate precipitation compared with the casein phosphopeptide (CPP) and the phosvitin phosphopeptide (PPP) having less than 65% dephosphorylation wherein the comparison shows that PPP is superior over CPP in solubilizing calcium (see above corresponding discussion), and have taught that phosphate content (i.e., dephosphorylation state) of the phosvitin phosphopeptide (PPP) has a critical effect on calcium binding ability thereby effect on said solubilization (see Fig,. 5, and page 993, right col., line 13 to page 994, left col. line 1).

In addition, Jiang et al. have compared phosvitin phosphopeptide (PPP) with casein phosphopeptide (CPP), and have shown that the PPP with 35% phosphate retention equivalent to the 65% dephosphorylated PPP is superior over said CPP (casein) with regard to inhibition of calcium phosphate precipitation, i.e., promoting satisfactory calcium solubilization (see Fig. 5 wherein "●" is CPP curve, and "■" is 65% dephosphorylated PPP curve). Jiang et al, explicitly teach that 35% phosphorylated (65% dephosphorylated) **phosvitin** can solubilize more calcium than CPP (**casein** phosphopeptide) (see page 994, left col., last 5 lines).

Since Reynolds' patent is directed to stable soluble calcium phosphate complex (col. 3, lines 14-18, and patent claim 1, line 1) mediated by the casein phosphopeptide, and since the phosvitin (CPP) is superior over casein (CPP) to inhibit precipitation thereby promote the solubilization of calcium thereof as taught by Jiang et al., and thereby increase calcium bioavailability for pharmaceutical application (see above), one of ordinary skill in the art would have chosen the phosvitin phosphopeptide (PPP) to produce the calcium phosphate complex.

Since the phosphorylation/dephosphorylation state of phosvitin peptide is critical for forming soluble (or preventing/inhibiting insoluble) calcium phosphate, and since it has been found that the 65% dephosphorylated phosvitin (PPP) is superior over casein (CPP) (see above), one of ordinary skill in the art would have TRIED to substitute the phosvitin phosphopeptide with 65% dephosphorylation for the casein phosphopeptide in the Reynolds' composition, and would have also tried to administering And, also, When tried, it would have necessarily led to reasonable expectation of success. Therefore, combination of the references' teachings renders the claims *prima facie* obvious.

The applicant's response to the 103 rejection above

At pages 7 and 8, the response filed 5/19/10 submits that the Reynolds' composition is an oral composition which is patentably distinct from the instant pharmaceutical composition in view of the restriction requirement. The response assert that the amendment of claim 46 and 186 to change "comprising" to "consisting essentially of"; this amendment would render the Reynolds' complex comprising the phosphopeptide and amorphous calcium phosphate (ACP) non-obvious over instant composition of claims 46 and 186 (p.7, response). Thus, the response infers that there is no suggestion or motivation in the references to make the combination that renders the instant compositions prima fascia obvious; and therefore, the response requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because of the reasons set forth in above rejection, and the reasons below.

Reynolds teaches a pharmaceutical composition comprising pharmaceutical acceptable carrier (col.7, line 4-7) is not necessarily a formulated oral compositor (inspire of usefulness in oral application). The restriction requirement mailed 3/27/06 set forth that claim 106 and dependent claims thereof drawn to the oral care product (composition) which is an oral care device and dental floss (see original claims 106-108, for example) and which is not contained in the Reynolds' pharmaceutical composition; and thus, the Reynolds' composition is obvious over instant pharmaceutical composition.

Like "comprising", "comprising" to "consisting essentially of" is considered to be open-ended claim language; and thus, the Reynolds' teachings of the "complex" comprising the phosphopeptide such as phosvitin peptide and ACP read on the instant claims.

The combination of Reynolds and Jiang et al. teachings renders the claims obvious. This is because, although Reynolds uses the casein phosphopeptides (SEQ ID NOs:2-4 which are all 20% dephosphorylated (see above), Reynolds has clearly suggested that the phosphopeptide can be obtained from any source that includes the known phosphor-acid rich proteins, phosvitin (col. 2, lines 58-60), and because Jiang et al. has taught that the phosvitin phosphopeptide (PPP) which is less than 65% dephosphorylated is superior the casein phosphopeptide (CPP) in solubilizing calcium phosphate precipitation, and have taught that the dephosphorylation state of the PPP has a critical effect on calcium binding ability solubility (see above). This, in turn, would increase calcium bioavailability for pharmaceutical application (see above rejection). Thus, one of ordinary skill in the art would have been motivated to substitute PPP for CPP in making/formulating a pharmaceutical composition such as nutraceutical comprising PPP (see p.994, left col., lines 10-12, and abstract, Jiang et al.) with reasonable expectation of success. Thus, the 103 rejection is proper and maintained.

[2] Claims 186, 194, 218 and 296 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds E. C. (US Pat. No. 6780844 B1) in view of Jiang et al. (*J. Agric. Food Chem.* (2000) 48, 990-994) as applied to claims 186 and 194, and further in view of Shuch et al. (US Pat. No. 6503483).

The teachings of claims 186 and 194 by Reynolds, Jiang et al. and Jacobson et al. have been set forth above.

Yet, these three references do not expressly teach that the formulated composition is in drop form.

Shuch et al. teach that oral delivery system, i.e., formulation can be candy-gum "drops" (see col. 8, line 62 to col. 9, line 2), as applied to claim 218 and 296.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate said composition as drops because "drops" refer to small quantity of the formulation of claims 218 or/and 296. In addition, choosing the "drops" formulation for delivery small quantity of the oral composition is well within purview of one of ordinary skill in the art when instant invention was made. The nexus between the "drops" form and the "pharmaceutical composition" taught by Reynolds is that both Shuch et al. and Reynolds teach that the composition is useful in oral application, wherein the "drops" are suitable for topical application (col. 9, lines 4-5, Shuch et al.). Therefore, the references' teachings are *prima facie* obvious over instant claims in the absence of any unexpected result.

The applicant's response to the 103 rejection above

At page 9, the response filed 5/19/10 submits that the type of drops in the claimed invention are not obvious over the prior art taught by Shuch. The teaching by Shuch does not make up for the deficiencies of Reynolds, Jiang et al. as discussed above. Thus, the response requests withdrawal of the rejection.

This is found unpersuasive because the reasons for the combination teachings of Reynolds, Jiang et al. rendering the claimed invention *prima facie* obvious has been discusses above, and because, given current state of the art, choosing the "drops" formulation is well within purview of one of ordinary skill in the art such as dentistry without unexpected result. Therefore, the 103 rejection above is maintained.

Conclusion

Claims 46, 49-52, 186, 194-198, 217-220, 246, 280, 282-285, 289-292 and 295-299 are not allowed. Claims 53, 199, 281, 286-288, 293 and 294 are objected to as being dependent upon a rejected base claims 46 and 186, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 272 and 273 are free from the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any comments considered necessary by applicants must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Samuel Wei Liu, Ph.D. whose telephone number is (571) 272-0949. The Examiner can normally be reached daily except alternate Fridays from 8:30 A.M. to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor Manjunath N. Rao can be reached at (571) 272-0939. The official fax number for Technology Center 1600 is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656

/ANAND U DESAI/

Primary Examiner, Art Unit 1656

August 1, 2010